5-Acetoacetyl-2-furoates by Friedel–Crafts Acetylation of Methyl and Ethyl 2-Furoates

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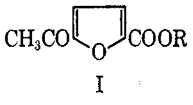
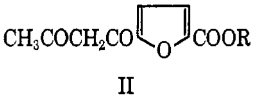
The reaction of methyl and ethyl 2-furoates with acetic anhydride and stannic chloride is reported[1-3] to give the corresponding 5-acetyl-2-furoates (I). We have now observed that, under the conditions described in the literature, the so far unknown 5-acetoacetyl-2-furoates (II) are frequently the main products obtained. The formation of keto esters (I) prevails only in short-time, low-conversion reactions. Diketo esters (II) are present also in this case in a significant amount.



I



II

R = CH_3, C_2H_5

Table I gives an account of the analysis and melting points of the four esters and of the two corresponding acids (A and B) obtained by us.

It is worth noting that the elemental analysis does not permit a clear-cut distinction between keto esters and diketo esters. Moreover a comparison between the melting points found in this work and those reported by some authors (see Table I) suggests that the compounds frequently described as keto esters were actually the now recognized diketo esters.

The structure of the D and F compounds is completely supported by chemical and spectrographic evidences. They dissolve in cold aqueous sodium carbonate and are regenerated by the prolonged action of carbon dioxide. A copper chelate is obtained by the usual procedure. Prolonged boiling of the two diketo esters with diluted hydrochloric acid gives acetic acid and the true 5-acetyl-2-furoic acid A.

The infrared spectra of the carbon tetrachloride solution of diketo esters do not show the strong band at 1700–1670 cm^{-1}, which is usually present in the spectra of the conjugated ketones. A broad, very strong band near 1610 cm^{-1} and a very broad weak band near 2700 cm^{-1} are present, both of which are characteristic of β-diketones. The formation of β-diketo ester and the appearance of a broad band at 1610 cm^{-1} probably explain why Yamaguchi[4] and Kubota[5] did not interpret the infrared spectrum of the supposed ethyl 5-acetyl-2-furoate.

The nuclear magnetic resonance (nmr) spectrum of the methyl 5-acetoacetyl-2-furoate (5% solution in carbon tetrachloride) confirms that this compound is a furan derivative substituted in positions 2 and 5 completely in keto enolic form. The chemical shifts (δ in parts per million from tetramethylsilane), the multiplicities, the integrated intensities, and the related groups follow: 2.14, singlet, three, CH_3CO (keto); 3.83, singlet, three, OCH_3 (ester); 6.11, singlet, one, =CH (enol); 7.07, a part of AB pattern, one, H-3 furan proton; 7.03, a part of AB pattern, one, H-4 furan proton; 15.20, very broad peak, one, OH (enol). The J_{34} coupling constant is 3.6 cps.

The 5-acetyl-2-furoic esters absorb near 1722 (ester C=O group conjugated with a heterocyclic nucleus) and near 1679 cm^{-1} (keto C=O group conjugated). Alkaline hydrolysis gives the correct saponification equivalent and 5-acetyl-2-furoic acid is obtained therefrom in almost quantitative yield. Analyses of the oximes further confirm the structures.

Both 5-keto- and 5-diketo-2-furoic acids may be oxidized, under suitable conditions, to 2,5-furandicarboxylic acid.

TABLE I

5-ACETYL-2-FUROIC ACID, 5-ACETOACETYL-2-FUROIC ACID, AND THEIR METHYL AND ETHYL ESTERS

No.	Compound	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Mp, °C Present work	Mp, °C Lit.
A	5-Acetyl-2-furoic acid	54.55	54.39	3.92	3.85	206–207	Decompn at 230,[a] 198[b]
B	5-Acetoacetyl-2-furoic acid	55.11	54.89	4.11	4.33	228–229 dec	
C	Methyl 5-acetyl-2-furoate	57.13	56.90	4.79	4.93	101–102	112–113,[c] 104,[d] 112[e]
D	Methyl 5-acetoacetyl-2-furoate	57.14	57.20	4.79	4.90	111–112	
E	Ethyl 5-acetyl-2-furoate	59.34	59.70	5.53	5.82	71–71.5	85–86[a,b]
F	Ethyl 5-acetoacetyl-2-furoate	58.92	58.98	5.39	5.67	87–88	

[a] Reference 1. [b] Reference 3. [c] Reference 2. [d] E. Votocek and A. Kroslak, *Collection Czech. Chem. Commun.*, **11**, 47 (1939); *Chem. Abstr.*, **32**, 4983 (1939). [e] G. G. Galust'yan and I. P. Tsukervanik, *Zh. Obshch. Khim.*, **34**, No. 5, 1478 (1964).

Experimental Section[6]

Methyl 5-Acetoacetyl-2-furoate.—Stannic chloride (130 g, 0.5 mole) was added dropwise, over a period of 90 min, to a stirred mixture of 31.5 g (0.25 mole) of methyl 2-furoate and 102 g (1 mole) of acetic anhydride cooled to 2°. During the addition the temperature never exceeded 10°. After standing overnight at room temperature, the mixture was cooled to 0–2°, hydrolyzed by stirring for 3 hr with 20 ml of 30% hydrochloric acid, and poured in 200 ml of water. The liquid was repeatedly extracted with benzene; the combined organic layers were washed many times with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The brown residue was sublimed at 60–70° (0.25 mm) in a great finger-type sublimator. The sublimate (30 g, 58% yield) is methyl 5-acetoacetyl-2-furoate of fairly good purity. Further purification of the product for the analysis was obtained by crystallization of a sample from ethanol. Melting point and analysis are given in Table I. An alternate route to the β-diketo ester of better purity consists of extracting the benzene layer many times with concentrated

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(1) H. Gilman and N. O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).

(2) G. Modena and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **13**, 72 (1955).

(3) P. A. Finan and G. A. Fothergill, *J. Chem. Soc.*, 2723 (1963).

(4) M. Yamaguchi, *Bunseki Kagaku*, **7**, 211 (1958).

(5) T. Kubota, *Tetrahedron*, **4**, 82 (1958).

(6) Microanalyses were performed by Alfred Bernhardt, Mülheim, West Germany. Melting points (open capillaries) and boiling points are not corrected. Infrared spectral data were obtained with a Perkin-Elmer Model 221 spectrophotometer equipped with sodium chloride prisms. Nmr spectra were determined using a Varian HA-100 spectrometer with tetramethylsilane as an internal standard.

aqueous sodium carbonate at room temperature and then bubbling carbon dioxide in the aqueous solution for several hours, whereby the salt of the enolic form of the diketo ester is quantitatively decomposed. The copper chelate was prepared by addition of 2 g of the β-diketo ester in ethanol solution to an excess of copper acetate dissolved in 50% ethanol and extraction with chloroform. After recrystallization from benzene the melting point was 252.5–253.5°.

Anal. Calcd for $C_{20}H_{18}O_{10}Cu$: C, 49.85; H, 3.76; Cu, 13.18. Found: C, 49.69; H, 3.61; Cu, 13.08.

Ethyl 5-Acetoacetyl-2-furoate.—This ester was prepared through two different ways.

(1) By the aforementioned procedure the ethyl ester was prepared with similar results, but the yield was slightly lower because more difficulties were experienced in the sublimation of the low melting brown residue. Melting point and analysis are given in Table I. The copper chelate, obtained under the same conditions as above, melted at 234.5–235.5°.

Anal. Calcd for $C_{22}H_{22}O_{10}Cu$: C, 51.85; H, 4.35; Cu, 12.46. Found: C, 52.02; H, 4.46; Cu, 12.61.

(2) When the reactions was carried out as originally proposed by Gilman, *et al.*,[1] (benzene as solvent, 250 ml; ethyl 2-furoate, 56 g, 0.4 mole; acetic anhydride, 40.8 g, 0.4 mole; stannic chloride, 208.5 g, 0.8 mole; molar ratios 1:1:2) keeping the temperature at 13–20° and hydrolyzing the reaction mixture 90 min after the addition of stannic chloride, the crude mixture contained much unreacted ethyl 2-furoate, chiefly ethyl 5-acetyl-2-furoate and ethyl 5-acetoacetyl-2-furoate, and little higher boiling products.

By fractional distillation under reduced pressure were collected at 85–120° at 20 mm 44 g of ethyl 2-furoate unreacted and at 100–150° (0.1–1 mm) 11 g of the keto and β-diketo esters. The infrared quantitative analysis of the mixture showed that approximately a 2:1 ratio was obtained. The two components were actually separated by repeatedly stirring the benzene solution with aqueous sodium carbonate and regenerating the β-diketo ester by bubbling carbon dioxide for several hours into the aqueous layer; 3.5 g of ethyl 5-acetoacetyl-2-furoate (4% yield) was recovered.

Methyl or Ethyl 5-Acetyl-2-furoate.—The keto esters were obtained by the short time reaction as described in method 2 above, it being difficult to obtain them in the pure state under the reaction conditions usually described in literature (very long reaction time). For the ethyl 5-acetyl-2-furoate the benzene layer, previously exhausted with aqueous sodium carbonate, was dried and evaporated under reduced pressure. The residue (7 g, 10% yield) was sublimated and the sample for the analysis was further purified by crystallization from ethanol. Analyses and melting points of the keto esters are given in Table I.

Anal. Calcd for $C_8H_8O_4$: equiv sapon, 168.15. Found: equiv sapon, 169. Calcd. for $C_9H_{10}O_4$: equiv sapon, 182.2. Found: equiv sapon, 182.5.

The presence of the ketonic group was also substantiated by the preparation of the oximes. The white oxime of methyl 5-acetyl-2-furoate after recrystallization from water melted at 89.5–93.5°.

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.35; H, 5.00; N, 7.47.

The oxime of ethyl 5-acetyl-2-furoate after crystallization from 35% ethanol melted at 129–131°.

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.11. Found: C, 54.99; H, 5.71; N, 7.41.

5-Acetoacetyl-2-furoic Acid.—The hydrolysis of the β-diketo esters to the corresponding acid required some caution because of the easy splitting of the acetoacetyl group and therefore it was not a clear-cut reaction. Ethyl 5-acetoacetyl-2-furoate (3.03 g) was dissolved in 30 ml of 1 *N* sodium hydroxide and warmed to 95–98° for 15 min. After cooling carbon dioxide was bubbled into the solution until the formation of the precipitate was stopped. On filtration, 0.45 g of the unaltered diketo ester was collected. The solution was then acidified with a little excess of 1 *N* hydrochloric acid; after filtration and drying, 1.58 g of crude impure acid was obtained (yield *ca.* 70%). By crystallization from 220 ml of boiling water, 0.87 g of pure 5-acetoacetyl-2-furoic acid was obtained (mp 228–230° dec).

5-Acetyl-2-furoic Acid.—The keto ester was hydrolyzed by refluxing the alcoholic solution with 100% excess of sodium hydroxide 1 *N* in water–ethanol solution. After gentle boiling for 1 hr the solution was evaporated under reduced pressure. The residue was diluted with a small quantity of water, filtered, and acidified. The acid was collected and recrystallized from water–ethanol. Analysis and melting point are given in Table I.

Anal. Calcd for $C_7H_6O_4$: neut equiv, 154.1. Found: neut equiv, 154.

Note.—While this paper was ready for publication, we became acquainted with the surprising results obtained by G. C. Robinson[7] on the directive effects in acylation of methyl furan-2-carboxylate. Although we agree that the reaction is more complex than was previously assumed, we can confirm that, at least in the acylations with acetic anhydride, significant amounts of furan derivatives acylated in position 4 cannot be isolated and identified among the reaction products. We will refer to the results obtained with other anhydrides in a subsequent Note.

Registry No.—A, 13341-77-0; B, 13341-78-1; C, 13341-79-2; oxime of C, 13341-80-5; D, 13341-81-6; E, 13318-36-0; oxime of E, 13341-82-7; F, 13341-83-8.

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(7) G. C. Robinson, *J. Org. Chem.*, **31**, 4252 (1966).

Synthesis of Oxetanes by Photoaddition of Benzophenone to Furans

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The direct 1,2 photoaddition of benzophenone to furan was observed independently by two groups of workers[1] to lead an oxetane. The product was later identified unequivocally by nuclear magnetic resonance (nmr) as the 6,6-diphenyl-2,7-dioxabicyclo[3.2.0]-Δ^3-heptene (**1**).[2] We have carried out the photoaddition of benzophenone to 3-methylfuran, 2-methylfuran, 2-furfuryl alcohol, and 2,4-dimethylfuran. The results of the irradiations of solutions of benzophenone in each one of these furans are shown in Table I.

In contrast to the product mixture of the two isomeric oxetanes obtained by Toki, Shima, and Sakurai[3] from the photolysis of aldehydes such as benzaldehyde, acetaldehyde, and propionaldehyde in 2-methylfuran which result from addition of the carbonyl compound to either double bond of the furan, we have in each case isolated one single product. It is interesting to note that in this work benzophenone invariably adds to the double bond having the methyl substituent and, if the furan carries two methyl groups as in 2,4-dimethylfuran, the resulting product mixture consists of 50% bicyclic adduct to one double bond and 50% bicyclic adduct to one double bond and 50% bicyclic adduct to the other. Apart from the oxetanes no

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(1) G. O. Schenck, W. Hartmann, and R. Steinmetz, *Ber.*, **96**, 498 (1963); G. S. Hammond and N. J. Turro, *Science*, **142**, 1541 (1963).

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